REMARKS

Claims 1, 10, 12-14, 16-18, 29, 30, 32, 33, 35-38, 40, and 42-57 are pending in the present application.

The rejections of: (a) Claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49, and 55-57 under 35 U.S.C. §103(a) over Gefter et al (US 6,180,608) in view of Bauer et al (US 2002/039996); and (b) Claims 38, 40-42, 58 and 60 under 35 U.S.C. §103(a) over Gefter et al in view of Bauer et al and Engel et al (US 5,663,145), are obviated in part by amendment and traversed in part.

In order to ensure completeness and clarity, Applicants remind the Examiner of the following. The present invention relates to a sustained release pharmaceutical administration form, as well as methods and kits, where the form is a pharmaceutical gel preparation containing D-63153. As the Examiner recognizes, Gefter et al fails to disclose or suggest D-63153.

Indeed, Gefter et al provides the therapeutic effectiveness of a pharmaceutically active peptide which seeks to be maintained *in vivo* over prolonged time periods to treat hormone-dependent diseases. To this end, Gefter et al disclose a pharmaceutical composition comprising a water-insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound in vivo upon administration of the complex. The peptidic compound of Gefter et al comprises peptides, polypeptides and proteins. The peptidic compound can also comprise an LHRH analogue which may be an LHRH agonist or an LHRH antagonist in a narrower sense, including the exemplary the LHRH antagonists PPI-149, PPI-258 and cetrorelix.

In Gefter et al, the carrier macromolecule comprises cationic carrier macromolecule like poly-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule

like polyalcohol derivatives, specifically polysaccharides and more specifically carboxymethylcellulose, algin, alginate, acetate polymers, acrylic polymers, alkali starch glycolate and others.

The current invention does not comprise a carrier macromolecule and does not use such carrier macromolecule. On the contrary the inventive peptide forms the administration form for sustained release itself.

Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149-CMC is already a sustained delivery complex. However, the present invention uses sodium chloride as an inorganic salt as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt.

In addition to acknowledging that Gefter et al fails to disclose or suggest D-63153, the Examiner recognizes that Gefter et al also discloses differing sodium chloride concentrations (Official Action pages 7-8, numbered paragraphs 9-10). However, the Examiner alleges that Bauer et al disclose a pharmaceutical administration form containing peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate and others.

Bauer et al discloses that peptides have a nature prone to uncontrolled aggregation and that the peptides if administered lead to a concentration-dependent lowering of the bioavailability from the peptide concentration. Bauer at al therefore disclose that addition of a free acid to the easily soluble peptide salt prevents that peptide salts prone to aggregation. The combination of the teaching of Gefter et al and of Bauer et al does not lead to the inventive subject matter.

Moreover, as recognized by the Examiner, Bauer et al does not actually disclose or suggest D-63153. The Examiner cites paragraph [0014] of Bauer et al, which states "The

peptides employed are the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix, and the antagonists according to the U.S. Pat. No. 5,942,493 and DE 19911771.3." These references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed.

Applicants wish to further note that the Examiner emphasizes that Bauer et al disclose a pharmaceutical administration form which contains peptides prone to aggregation. Bauer et al provide a teaching to *avoid aggregation* of the peptides whereas the presently claimed invention is a sustained release formulation and consequently involves the aggregation of peptides by reconstitution of lyophilized peptide salts with inorganic salts or acetic acid salts. Thus, the mechanism by which the claimed invention is achieved as compared to the cited are at direct odds and are incompatible. Therefore, Applicants submit that the teachings of Bauer et al are not relevant to the claims of the present application. It is only when Applicants disclosure is used as a guidepost to reconstitute the claimed invention with the benefit of hindsight that the disclosure of Geftner et al and Bauer et al are combinable. In all other proper circumstances, the skilled artisan would not find modification in the disclosure of Bauer et al to modify the disclosure of Geftner et al. Thus, the claimed invention is not obvious in view of the combined disclosures of Geftner et al and Bauer et al.

To further illustrate the beneficial results flowing from the claimed invention, Applicants direct the Examiner's attention to the Examples of the present application. In each of Examples 1-7, D-63153 is reconstituted in a solution of sodium chloride. Indeed, Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride. In Example 2, D-63153 reconstituted in 0.1% sodium chloride is shown to retain absolute bioavailability. Example 3 illustrates the testosterone-suppressing potential of D-63153 reconstituted in 0.1% sodium chloride. Examples 4-7 provide various

viscosity studies with D-63153 reconstituted in 0.1% to 0.2% sodium chloride, with Example 7 illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride. Geftner et al and Bauer et al do not disclose or suggest these illustrated effects and, as such, it cannot be fairly considered that such an effect would be expected.

"Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, the experimental data discussed above from the specification clearly illustrates that substantial benefits flowing from the claimed composition, which are enough to rebut even a *prima facie* case of obviousness.

In a further consideration the Examiner refers to the Engel et al, and alleges that the current invention in claims 38-42 and 58-60 is obvious. Applicants disagree for the reasons already of record, coupled with the evidence provided above. For sake of completeness, Applicants reassert the following with respect to the kit claims.

Engel et al teach a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The current invention claims in claims 38-42 and 58-60 relate a kit comprising an LHRH antagonist as finished preparation of the peptide compound and a solution of an inorganic salt or acetic acid salt for reconstitution. In view of the foregoing, the combination of the teaching of Gefter et al, Bauer et al, and of Engel et al does not lead to the inventive subject matter of the kit claims.

Despite the foregoing, the Examiner maintains the rejections over Gefter et al, Bauer et al, and Engel et al. Gefter et al disclose a pharmaceutical composition comprising a water-

insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound *in vivo* upon administration of the complex. The peptidic compound of Gefter et al comprises peptides, polypeptides and proteins, including LHRH analogues, such as LHRH agonists or antagonists.

However, Gefter et al fails to disclose or suggest the pharmaceutical compositions of the present invention. In particular, Gefter et al do not disclose or suggest the importance of using an aqueous solution of sodium chloride in the reconstitution of the active ionic peptide to form a gel, or of the concentrations of such salts for this purpose (0.01 to 0.9% w/v). Rather, Gefter et al disclose combining the active peptide with a carrier macromolecule (such as poly-L-lysine or other polymers, such as polyalcohol derivatives and polysaccharides) to form the gel preparation. In addition, Gefter et al do not disclose or suggest D-63153 or the concentrations of sodium chloride used for reconstituting it.

Gefter et al do disclose the use of a 0.9% sodium chloride solution as a reconstitution vehicle, in Example 14, to reconstitute the complex PPI-149-CMC, but this disclosure places no importance on the use of using an aqueous solution of sodium chloride in the reconstitution of the active ionic peptide to form a gel for sustained release. Rather, Applicants submit that PPI-149-CMC consists of a complex of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, which complex is already a sustained delivery complex.

The present invention uses sodium chloride as an inorganic salt as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt, without the need for the use of a carrier macromolecule. Thus, when reconstituted according to the present invention, the active ionic peptide contained in the pharmaceutical compositions of the present invention forms the administration form for sustained release itself.

Bauer et al disclose peptides that are naturally prone to uncontrolled aggregation and that the peptides, if administered, lead to a concentration-dependent lowering of the bioavailability from the peptide concentration. Applicants submit that Bauer et al disclose that the addition of a free acid to the easily soluble peptide salt prevents that peptide salt from being prone to aggregation. The disclosure of Gefter et al and the deficiencies thereof in the context of the present invention are discussed above, and Applicants submit that the disclosure of Bauer et al does not supplement the disclosure of Gefter et al in such a way as to lead to the present invention. Thus, Applicants submit that the combination of the disclosures of Gefter et al and Bauer et al would not lead a skilled person to the subject matter of the present invention.

In numbered paragraph 10, the Examiner alleges that Gefter et al combined with Bauer et al gives a reasonable expectation of success to substitute D-63153 for other GnRH antagonists and to obtain sustained delivery formulation. However, as set forth above, neither Gefter et al nor Bauer et al disclose the possibility to reach such sustained delivery formulation being a gel according to the invention.

The Examiner also cited Engel et al as allegedly disclosing a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The presently claimed invention relates to kit comprising an LHRH antagonist as a finished preparation of the peptide compound and a solution of sodium chloride for reconstitution. Applicants submit that a combination of the teaching of Gefter et al, Bauer et al, and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claim as proposed herein for the reasons already provided above.

Applicants further submit that it is a remarkable fact that Engel et al disclose a dosage regimen of the pharmaceutical composition in which lyophilisate ampoules are in the form of

an acetate and it is not intended to bring it in a slow release form according to the invention or are already in a slow release form and such slow release form is an embonate salt (and therefore in a suspended form) or the soluble peptide salt is embedded in microparticles (see column 2, lines 48-67). Such slow release form is not the starting form of the present invention.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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